Introduction

Diphtheria has been known since ancient times, although in the pre-microbiological age it was not clearly distinguished from streptococcal infections. The first accurate description of the disease was done by Bretonneau in 1826. Klebs described the morphological appearance of the organism in a diphtheritic membrane in 1883, and a year later Loeffler isolated the organism.

Diphtheria is a potentially acute disease caused by exotoxin-producing *Corynebacterium diphtheriae*. Morbidity and mortality result from the bacterial toxin that may cause obstructive pseudo-membranes in the upper respiratory tract (croup) or damage to myocardium and other tissues. Throughout history, diphtheria has been one of the most feared childhood diseases, characterized by devastating outbreaks. In countries endemic for diphtheria, the disease occurs mostly as sporadic cases or in small outbreaks. Although most infections with *C. diphtheriae* are asymptomatic or run a relatively mild clinical course, high case-fatality rates (>10%) have been reported even in recent outbreaks.

Before the introduction of antitoxin in the 1890s, case-fatality rates from some diphtheria outbreaks reached or exceeded 50%. Although antitoxin, tracheostomy and modern intensive care facilities have dramatically reduced case-fatality rates in diphtheria when the disease occasionally occurs in industrialized countries, lethality is still high in many developing countries.

Bacteriology

Diphtheria is an acute illness caused by toxigenic strains of *Corynebacterium diphtheriae*, a Gram-positive, non-sporing, non-capsulate slender club-shaped bacillus that exists in 4 biotypes namely *C. gravis, C. mitis, C. intermedias* and *C. belfanti.*

The exotoxin produced by *C. diphtheriae* acts locally on the mucous membranes of the respiratory tract or, less commonly, on damaged skin, to produce an adherent pseudomembrane. Systemically, the toxin acts on cells of the myocardium, nervous system and adrenals.

Mode of transmission

Humans are the only natural host for *C. diphtheriae*. The disease is communicable for up to 4 weeks, but carriers may shed organisms for longer. Spread is by respi ratory droplets or by direct contact with skin lesions or articles soiled by infected individuals. Effective antibiotic therapy promptly terminates shedding. The rare chronic carrier may shed organisms for 6 months. In developing countries, a high rate of skin infection caused by a diphtheriae creates a primary reservoir of diphtheriae organisms. Symptoms of respiratory diphtheria occur usually after an incubation period of 1–5 days.

Clinical Features

Diphtheria is a disease affecting the tonsils, the pharynx, the larynx, and the nose. In developing countries skin diphtheria is common with lesions indistinguishable from or a component of, impetigo. Although most infections are asymptomatic or run a relatively mild clinical course, some patients succumb to airway obstruction caused by laryngeal diphtheria or toxic myocarditis. The onset is relatively slow and characterized by moderate fever and a mild exudative pharyngitis. In severe cases, so called pseudo-membranes gradually form in the throat, recognizable by their typical asymmetric, greyish-white appearance and strong attachment to the underlying tissue. Such pseudo-membranes may extend into the nasal cavity and the larynx causing obstruction of the airways. Laryngeal diphtheria, which sometimes occurs even without pharyngeal involvement, is a medical emergency that often requires tracheostomy. Exotoxin absorbed from the mucosal (or cutaneous) lesions may account for toxic damage to organs such as the myocardium, kidneys and nervous system.

During outbreaks, clinical diagnosis based on typical pseudo-membranous pharyngitis is quite reliable. Although laboratory investigation of suspected cases is strongly recommended, treatment should not be delayed while waiting for the laboratory results. Bacterial culture is the mainstay of aetiological diagnosis.
Urgent treatment of diphtheria is mandatory to reduce complications and mortality. The mainstay of treatment is intramuscular or intravenous administration of diphtheria antitoxin. Antibiotics (penicillin or erythromycin) have no impact on established exotoxic lesions but limit further bacterial growth and the duration of corynebacterial carriage that often persists even after clinical recovery. Antibiotic treatment usually renders patients non-infectious within 24 hours.

Epidemiology

Global Situation

Diphtheria is still a significant child health problem in countries with poor childhood immunization coverage. Where childhood immunization coverage is high and natural boosting low, as in most industrialized countries, a large proportion of the adult population is gradually rendered susceptible to diphtheria as a result of waning nature of the immunity.

In temperate climates, most cases occur during the cold season; whereas in warm climates, transmission takes place throughout the year. In countries where diphtheria is still endemic, preschool and school-age children are most commonly affected. In most industrialized countries, endemic diphtheria has disappeared or become extremely rare. However, the importance of maintaining high vaccination coverage against diphtheria among both children and adults has been demonstrated by outbreaks of the disease in many parts of the world, notably in countries of the former Soviet Union during the 1990s.

Situation in Sri Lanka

Diphtheria is a notifiable disease in Sri Lanka. The last laboratory confirmed case was reported in 1996. Thereafter not a single case of diphtheria has been reported from the entire country. Active immunization against diphtheria by using DTP vaccine was initiated in 1961. Currently immunization against diphtheria is carried out by using pentvalent vaccine (DTwP-Hep B-Hib) , DT and aTd vaccines.

Diphtheria vaccine

The primary aim of diphtheria vaccination is to reduce incidence and severity of the disease among young children. It has been postulated that given high and sustained coverage, vaccination could eliminate diphtheria as a public health problem as in the case of Sri Lanka.

Diphtheria toxoid is prepared from cell-free purified diphtheria toxin treated with formaldehyde. It is a relatively poor immunogen, which, to improve its effictiveness, is usually adsorbed onto an adjuvant, either aluminium phosphate or aluminium hydroxide.

Characteristics of the Vaccine

Currently, diphtheria toxoid is almost exclusively available in combination with tetanus toxoid (T) as DT, or with tetanus toxoid and pertussis vaccine as DTP (the origin of the pertussis component often specified as whole-cell (wP) or acellular (aP)). Diphtheria toxoid may also be combined with additional vaccines, such as hepatitis B and *Haemophilus influenzae* type b.

Diphtheria vaccines are based on diphtheria toxoid, a modified bacterial toxin that induces protective antitoxin. Diphtheria toxoid combined with tetanus toxoid and pertussis vaccine (DTwP), has been part of the EPI since its inception in 1974. During the period 1980–2000, the total number of diphtheria cases reported globally was reduced by >90%. Following the primary immunization series, the average duration of protection is about 10 years. Protective immunity may be boosted through exposure to circulating strains of toxigenic *C. diphtheriae*. Where natural boosting does not occur, booster doses of diphtheria toxoid beyond infancy, early school age and school leaving were required to maintain protective immunity.

The recommended schedule for vaccination against diphtheria varies considerably between countries. According to the WHO EPI schedule, the primary series of DTwP- or DTaP-containing vaccines should be administered in 3 doses, starting as early as 6 weeks of age and given with a minimum interval of 4 weeks. Where resources permit, additional doses can be given after the completion of the primary series. Many national immunization programmes offer 1–2 booster doses, for example one at around 2 years of age and a second at around 5 years of age.

The acronym DTP, using capital letters, signifies child formulations of diphtheria and tetanus toxoid and pertussis-containing vaccines. The acronym aTd is used for adolescent/adult formulations which contain substantially lesser amounts of diphtheria toxoid.

Types of diphtheria containing vaccine preparations

- **Diphtheria-tetanus-whole cell pertussis vaccine (DTwP) -** Refer to chapter on pertussis
- **Diphtheria-tetanus-acellular pertussis vaccine (DTaP) -** Refer to chapter on pertussis
- **DTaP-HepB vaccine -** Refer to chapter on pertussis
- **DTwP-Hib vaccine -** Refer to chapter on pertussis
- **DTwP-Hep B-Hib vaccine -** Refer to chapter on Pertussis
- **DTaP-HepB-IPV-Hib** - Refer to chapter on Pertussis
- **(Adolescent/adult formulation) dTpa -** Refer to chapter on pertussis
- **Diphtheria-tetanus toxoids vaccine (adsorbed) DT**

Diphtheria and tetanus toxoids vaccine (adsorbed) is prepared by combining purified diphtheria toxoid and purified tetanus toxoid. The antigens are adsorbed onto aluminium phosphate as adjuvant.

Each 0.5 ml dose of DT contains diphtheria toxoid ≤ 25 Lf (≥30 IU) and tetanus toxoid ≥ 5 Lf (≥ 40 IU) adsorbed onto aluminium phosphate (Al $P0_4$) ≥ 1.5 mg.

- **Adolescent/adult formulation diphtheria and tetanus toxoids vaccine (adsorbed) aTd**

Diphtheria and tetanus toxoid vaccine adsorbed for adolescents and adults is prepared by combining purified diphtheria toxoid and purified tetanus toxoid. The antigens are adsorbed on to aluminium phosphate as adjuvant.

Each 0.5 ml dose of aTd contains diphtheria toxoid ≤ 5 Lf (≥2 IU) and tetanus toxoid ≥5 Lf (≥40 IU) adsorbed on aluminium phosphate ($AlP0_4$) ≥1.5 mg.

This vaccine, with a lower titre of diphtheria toxoid, is for immunization of children aged over 7 years and adults. This reduction of diphtheria toxoid titre.

minimizes reactogenicity at the injection site but is still sufficient to provoke an antibody response in older children and adults.

Indications

1. **Diphtheria, tetanus and pertussis vaccine preparations (DTwP or DTaP)**

- Primary course of immunization against diphtheria, tetanus and pertussis is recommended for all infants on completion of 2, 4 and 6 months of age, with a booster dose at 18 months of age, unless there is an absolute or temporary contraindication. If the primary course is interrupted, it should be resumed but not repeated, allowing appropriate intervals (minimum of 6 weeks) between the remaining doses.

- Vaccination of unimmunized older children against diphtheria, tetanus and pertussis who are less than 5 years of age.

2. Adsorbed diphtheria and tetanus vaccine (DT)

- This vaccine is used for primary immunization in place of DTwP or DTaP vaccine when immunization against pertussis is contraindicated.

- It is recommended for booster vaccination of children against diphtheria and tetanus at the age of 5 years (immediately before school entry). It should be given at least 3 years after the most recent dose of DTwP or DTaP vaccine.

3. Adolescent/adult formulation diphtheria and tetanus vaccine (aTd)

- This vaccine is for booster immunization of children over 7 years of age and adults. As per the national EPI schedule children aged 12 years (at Grade 7 in school) who have already received a primary course of DPT (and/or DT) will receive a dose of aTd.

Dosage & Administration

Refer to chapter on pertussis

Storage

Refer to chapter on pertussis

Cautions and contraindications

Refer to chapter on pertussis

Adverse Events

DTP

Refer to chapter on pertussis

DT

Transient fever, headache, malaise and local reactions may occur; a small painless nodule may form at the injection site but usually disappears without sequelae; severe anaphylactic reactions are rare; neurological reactions have been reported on rare occasions.

aTd

Adverse events following aTd are generally mild and confined to the site of injection. Some inflammation may occur together with transient fever, malaise and irritability. Occasionally a nodule may develop at the site of injection but this is rare.

Sources

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